## RENIN INHIBITION (BUT NOT PLASMA RENIN ACTIVITY) PREDICTS THE RESPONSE TO CONVERTING-ENZYME INHIBITORS IN CHRONIC HEART FAILURE.

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Converting-enzyme inhibitors (CEIs) are effective in both low-renin and high-renin heart failure (CHF). This finding suggests either that plasma renin activity (PRA) is not an accurate measure of renin-angiotensin activity or that CEIs exert non-renin effects (e.g., through kinins). To distinguish between these two possibilities, we compared the effects of a renin inhibitor (enalkiren [EKR], 1.0 mg/kg i.v.) and a CEI (captopril [CPT], 25 mg orally) in 9 CHF patients. Unlike CPT, EKR exerts inhibitory effects only on the renin-angiotensin system. All patients received EKR first and CPT 24 hr later. Cardiac index (CI, l/min/m$^2$), stroke volume index (SVI, ml/m$^2$), mean arterial (MAP), LV filling (LVFP) and mean right atrial pressures (RA, mm Hg), systemic vascular resistance (SVR, d-s-c) and PRA (ng/ml/hr) were measured before (pre) and after (post) each drug; where * = $p < 0.05$ (pre vs post):

| | | CI | SVI | MAP | LVFP | RA | SVR | PRA |
|---|---|---|---|---|---|---|---|---|
| EKR | Pre | 2.2 | 28 | 82 | 28 | 13 | 1437 | 6.4 |
| | Post | 2.5* | 35* | 68* | 20* | 11* | 1024* | <0.2* |
| CPT | Pre | 2.2 | 30 | 78 | 27 | 13 | 1338 | <0.2 |
| | Post | 2.5* | 36* | 65* | 20* | 10* | 1013* | <0.2 |

Despite the absence of measurable PRA 24 hr after EKR, CPT produced hemodynamic effects similar to EKR. Interestingly, changes in LVFP and MAP after EKR were closely correlated with changes in LVFP and MAP after CPT (r=0.77 and r=0.74, respectively). In contrast, values for PRA measured before EKR did not predict the effect of either CPT or EKR on any hemodynamic variable (all r values 0.10 to 0.45, p=NS).

In conclusion, the ability of renin inhibition (but not PRA) to predict the acute response to CPT suggests that CEIs act primarily through the renin-angiotensin system (and not through kinins), but that the activity of this system cannot be accurately assessed by the measurement of PRA.

## LOCAL TOLERANCE DEVELOPMENT INHIBITS THE UPTAKE OF TRANSDERMAL NITROGLYCERIN.

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Previously, we have demonstrated that healthy subjects who carry a nitroglycerin (GTN) patch, had a three-fold increase in plasma GTN concentration during exercise. This could be caused by an increased diffusion from the patch, by increased uptake through local vasodilation or by reduced nitrate metabolism. In the present study, ten volunteers first carried a 10mg GTN patch for two hours. Immediately after patch removal, they exercised on a bicycle ergometer. An increase in plasma GTN concentration was found (1.4 to 2.1 nmol/l, borderline sign., p=0.06). If local vasodilation were the cause of the exercise-induced GTN increase, vessel reactivity might be modified over time. After 24 hours of transdermal GTN administration, the subjects had only a small, non-significant increase in GTN concentration during exercise with patch on (1.4-1.6nmol/l). The patch was then removed and a new one was placed on a contralateral site. Two hours later repeat exercise increased plasma GTN-concentration from 1.4 to 2.3 nmol/l ($p<0.001$).
Thus, GTN uptake during exercise seems to be locally regulated. After 24 hours treatment, development of local tolerance inhibits the exercise-induced increase in nitrate uptake.

## DEFECTIVE VENOARTERIOLAR REFLEX AS A POSSIBLE CAUSE FOR ANKLE OEDEMA FOLLOWING NIFEDIPINE THERAPY

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Ankle oedema is not an uncommon side effect of nifedipine (nif.) therapy . To evaluate the possible effect of nif. on the microcirculation, 18 patients with systemic hypertension (SH) who were known to develop ankle oedema after nif. (group 1) and 19 patients with SH who did not develop ankle oedema after nif.(group 2)were studied. Following 4 weeks of nif. therapy(10 mg ,three times daily), the microcirculation on the dorsum of the foot was measured using Laser-Doppler flowmetry(Laserflo,USA). Estimation of the microcapillary flow was made both after supine resting (RF) and on standing upright (SF). The veno-arteriolar reflex(VAR) was calculated as SF in percentage of the RF.

RESULTS

| | Before nif. | | | After nif. | | |
|---|---|---|---|---|---|---|
| | RF | SF | SF/RF | RF | SF | SF/RF |
| group 1 | 0.54 | 0.45 | 83.6 | 0.78 | 0.75 | 96.2 |
| group 2 | 0.52 | 0.44 | 84.6 | 0.76 | 0.6 | 79.8 |
| p-value | >0.4 | >0.6 | >0.6 | >0.5 | 0.0001 | <0.0001 |

Thus the microcapillary flow did not decrease upon standing in patients who developed ankle oedema following nif. therapy indicating abnormal VAR. This may explain why ankle oedema develops in such patients following nifedipine therapy.

## A MULTICENTER DOSE RESPONSE STUDY OF SUSTAINED RELEASE DILTIAZEM HYDROCHLORIDE IN ANGINA PECTORIS

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Diltiazem sustained release (DSR) is effective given BID in patients (pts) with hypertension and angina pectoris (AP). However, the dose response relationship of DSR in patients with AP is not known. In a multi-center parallel design study, 224 pts with AP received single blind placebo (PL) BID for 1 week. Patients with reproducible angina and ≥ 1 mm ST segment depression (n=196) using a Mod. Bruce ETT were randomly assigned to a treatment group (PL, 60, 120, 180 or 240 mg DSR BID) and repeat ETTs were performed at 11 - 13 hours post-dose at the end of 3 weeks treatment. 149 pts met all protocol requirements and completed the study. Changes at the end of double-blind treatment in comparison to respective baseline values were:

| | PL | DSR BID | | | |
|---|---|---|---|---|---|
| | (n=30) | 60mg (n=31) | 120mg (n=25) | 180mg (n=29) | 240mg (n=34) |
| ETT Duration | 0.17 | 1.05 | 1.33* | 1.25* | 1.18* |
| Time to 1mm ST$_d$ | 0.86 | 1.70 | 1.14 | 1.84 | 1.90* |
| AP Episodes/Wk | -1.07 | -2.94 | -3.29 | -3.48 | -3.88* |

ETT duration and time to 1 mm ST$_d$ is in minutes, WK = week.
* = P<0.05 compared to double blind placebo.

Thus, treatment with 60 to 240 mg DSR BID increased ETT duration, reduced angina frequency and exerted favorable effects on ST segment depression, but a statistically significant dose response relationship was not documented. DSR was well tolerated with some increases in adverse effect incidences as dosage increased. This study shows that doses between 120 and 180 mg BID are optimum for antianginal therapy.